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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/937,756	09/25/97	RUEGER D	CRP-070FWCN2

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1645	9

DATE MAILED: 03/18/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/937756	Prueger et al.
Examiner	**Group Art Unit**
Hayes	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 12/18/98.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 82-104 is/are pending in the application.

Of the above claim(s) 83, 89, 92, 95, 98, 101 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 82, 84-88, 90-91, 93-94, 96-97, 99-100, 102-104 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 82-104 were ~~are~~ subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachm nt(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☒ Notice of Reference(s) Cited, PTO-892

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948 ~~sublet~~.

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 82, 84-88, 90-91, 93-94, 96-97, 99-100 & 102-104 in Paper No.8 is acknowledged.

The traversal is on the ground(s) that the inventions are "linked by common elements necessary to patentability of the claims in each group", and that "a search of the relevant art for the claims of Group I necessarily likely (*sic*) would include a search of the art for the claims of Group II". In contrast to Applicants' assertions, each of the different methods of Groups I-II possess different requirements that make them distinct, in which neurons are required to be treated in Group I, versus the different cell type of glial cells that are affected in the disease state of Group II.. The requirement is still deemed proper and is therefore made FINAL, for the reasons previously made of record.

Claims 83, 89, 92, 95, 98 & 101 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 94-104 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 13-23 of copending Application No. 08/937,755. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 82-93 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 08/937,755. Although the conflicting claims are not identical, they are not patentably distinct from each other because only a larger Markush group is being recited in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

4. Claims 82, 84-88, 90-91, 93 & 103-104 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No conception nor proper antecedent basis is apparent for a sequence having "at least 70% / greater than 60%... from the *C-terminal seven-cysteine* skeleton... residues *38-139*" (i.e., versus "*the amino acid sequence defining* the *conserved six cysteine* skeleton of hOP-1 (e.g., residues *43-139* of SEQ ID NO. 5)", as disclosed on page 53 of the specification (i.e., as it relates to claims 82, 84, 88, 90-91 & 93); thereby, constituting new matter.

No conception nor proper antecedent basis appears in context of that disclosed within the specification for the recitation, "complexed with at least one morphogen *pro* domain polypeptide..." (i.e., as it relates to claims 103-104). In other words, the mere existence of a *pro* domain on OP-1 is not of equivalent scope to adding multiple, or different, polypeptide *pro* domains to any polypeptide; thereby constituting new matter.

No conception nor antecedent basis appears in context of that disclosed within the specification for "treating", "restoring motor function", or "preserving motor function" in a

mammal afflicted with ALS or spinal cord injury. In contrast, page 3 of the specification (i.e., the Background of the Invention) merely mentions that ALS and spinal cord injury are neuropathic conditions, which lead to neural cell death. Moreover, original claims 10 & 39 solely encompass a method "for enhancing survival of neural cells at risk of dying" or "maintaining a [nonspecified] neural pathway"; thereby constituting new matter.

5. Claims 82, 84-88, 90-91, 93-94, 96-97, 99-100 & 102-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to a method of using OP-1 of SEQ ID NO: 4 or 5 to induce N-CAM and L1 expression in NG-108 cells, does not reasonably provide enablement for "treating/preserving motor function/restoring motor function" in a mammal afflicted with ALS/spinal cord injury, or for using structurally uncharacterized morphogens or biologically functional equivalents thereof to accomplish such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses that the human and mouse OP-1 of SEQ ID NOs: 5 & 6 are the preferred morphogens of the instant invention. The sole guidance provided by the specification concerning induction of neurite outgrowth is described on page 82, in which a 12 mm gap is traversed in a rat sciatic nerve graft experiment using a silicone tube filled with OP-1 gel, yet in which one graft site containing *no* OP-1 also showed axonal growth of 12 mm (i.e.,

axonal growth for 12 mm is not dependent on OP-1). Page 3 of the specification then summarizes the state of the art in which "[c]urrently, no satisfactory method exists to repair the damage caused by these neuropathies, which include multiple sclerosis, amyotrophic lateral sclerosis (ALS)...".

The state of the art is also as follows:

I) Lein et al. (ref# C18; Abstract, pg. 597) state "OP-1 requires NGF as a co-factor...in optimal concentrations". Lines 23-25 in the 2nd column of Lein (pg. 597) then teach that "[I]ndeed, the only trophic factor that has been clearly implicated in the regulation of the initial stages of dendritic growth is nerve growth factor (NGF)." In other words, without NGF there is no neurite outgrowth/synaptic contact/motor function. Without OP-1 there is still outgrowth in culture. Therefore, OP-1 is inert.

ii) Varley et al. state that "OP-1 [i.e., the preferred morphogen of the instant invention] *does not act on a postmitotic cell population*"[emphasis added] (see pgs. 441-442). Therefore, because neurons, by definition, are postmitotic/amitotic after birth, this reference clearly establishes that the instant invention can not work *in vivo* in a mammal without undue experimentation to determine otherwise; thereby, not being enabled.

iii) Wilson et al. (ref.# C33) disclose that BMPs, in general and as broadly claimed, do not predictably enhance "preserving/ restoring" synaptic contacts/motor function because, conversely, BMP-4 is a "neural inhibitor" (e.g., pg. 331, Abstract).

iv) Withers et al. (ref.# C34) state that "no synaptic contacts were observed", which is the result of "two possibilities: 1) the OP-1 [i.e, the preferred embodiment of the instant invention] induced dendrites were not receptive to innervation; or 2) the poor growth of axons in these cultures prevented normal synaptic contacts from occurring". In other words, *in vitro* culturing of sympathetic neurons (i.e., in 1996 vs. the 1991 claimed priority date of the instant invention) provides no nexus for how to administer a putative protein that may or may not affect neurons *in vivo*; nor how to assess when, *or if*, the invention works *in vivo*; especially when no adequate guidance is provided within the specification to extrapolate to such treatment, which involves motorneurons versus sympathetic neurons. In fact, Withers et al. appear to establish that the claimed invention does not work *in vitro*, and by analogy does not work *in vivo,* without undue experimentation to determine otherwise.

v) Jackowski (ref.# C14) teaches that CNS neurons do not regenerate (pg 305, last *pp).* In other words, because the minimal requirement for restoring/preserving synaptic contacts/motor function is that *de novo* axonal cell growth be completed for a sufficient distance to re-establish a proximity relationship to the prior target, no reasonable expectation of success is accepted in the art. It is noted that neuropathy/spinal cord injury, by definition, lose synaptic contacts and degenerate due to normal Wallerian degeneration (e.g., see Jackowski, pg. 304). Accordingly, regeneration/restoration of synaptic contacts/motor function does not occur either because processes fail to grow the necessary distance, they are in competition with other nearby

neuronal processes not derived from the affected nerve, scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, pgs. 309-310).

vi) Dead neurons characterize neurodegenerative diseases, such as ALS or spinal cord injury. Therefore, restoring or preserving motor function does not occur, as claimed. Thus, the claims are not commensurate in scope with that disclosed within the specification for treating neurodegenerative disease states or spinal cord injury, in general, and as such, merely constitutes an invitation to experiment to discover if Applicants' invention works *in vivo*.

vii) The non-neuronal tumor cell line, NG108-15, is not neuronal tissue, nor amitotic neurons, nor representative of any *in vivo* nervous system tissue. Nor are any appropriate neuro-specific assays provided in the instant specification to distinguish those putative "morphogens" from different proteins which do not have the desired activity of the instant invention, as it relates to affecting any neuronal populations; especially *in vivo*.

viii) *In vitro* tissue culture of non-neuronal tumorigenic cells provides no nexus to extrapolating to effective *in vivo* treatment of mammals, because no neural pathway are present in cell cultures, NG108 cells do not die, and these tumorigenic cells continue to proliferate, unlike neurons. Further, stimulation of N-CAM or L1 production is not equivalent to "treating" ALS or spinal cord injury, or for providing reasonable guidance toward restoring or preserving motor function.

Similarly, no adequate guidance is provided in the specification on how to successfully practice the full scope of the invention "in a mammal", as currently claimed, because it is further

unknown what metes and bounds are envisioned by the recitation, "treatment", and because no *in vivo* models are known, or adequately described, by which the skilled artisan could extrapolate "how to use" the invention "in a mammal" with any reasonable expectation of success, for the reasons indicated above. Additionally, it is well accepted in the art the differences exist between *in vitro* protocols and results, versus *in vivo* protocols and results, especially as it relates to undefined parameters that do not distinguish when "treatment" is effective, or that require passage across the blood brain barrier which is impermeable to protein molecules/morphogens, or that involve undefined parameters that do not distinguish "treatment" of "ALS", for example, from any different disease state. The instant specification has also failed to disclose how these parameters are to be determined, how a similar method was practiced in the art with a different agent or to provide even a single working *in vivo* example of the claimed method. Additionally, it is not known at what point during any given disease state when treatment is recommended, or how one skilled in the art knows when, or if, they have successfully practiced the instant invention; thereby, requiring undue experimentation to discover how to successfully practice Applicants' invention. Further, it is unknown, nor disclosed, what specific aspects/symptoms of these claimed neurological disorders are envisioned to be "treated" (i.e., as it relates to claims 82, 84, 94 & 96), or what constitutes a therapeutically effective amount of the structurally deficient/uncharacterized morphogens claimed, or how to assay such *in vivo*. In other words, one skilled in the art would not reasonably be able to successfully make and use the invention, as claimed, without undue experimentation to determine such.

Lastly, the name "morphogen" as it relates to the generic sequences claimed, or to the recitation of the name alone (i.e., as it relates to claims 94, 96-97, 99-100 & 102-104), sets forth little or no structural characteristics, and little functional characterization. The specification does not teach which specific amino acids are critical for any morphogen function, nor how to distinguish such from any different polypeptide sequences that possess none of the desired functions of the instant invention, yet are encompassed by the claims. For example, cysteines alone would not be expected to possess any desired biological activity (i.e., as it relates to the generic sequences recited). Moreover, random mutations, substitutions, insertions, deletions, or biologically functional equivalents of different morphogen molecules would be expected by the skilled artisan to conversely result in inactive proteins, especially when "reduced" (i.e., as it relates to how "morphogens" are defined on pages 26 & 28-54 of the specification). For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger then states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification, as to what minimal structural requirements are necessary for determining how to make and use any "biologically functional equivalent" morphogen in the proposed method of the instant invention, would prevent the skilled artisan from determining when they are in possession of the necessary

components for practicing the invention, because random mutations of any protein would be expected by the skilled artisan to adversely affect the three-dimensional conformation of these molecules, without undue experimentation to determine otherwise.

6. Claims 82, 84-88, 90-91, 93-94, 96-97, 99-100 & 102-104 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is ambiguous why the physically and functionally distinct "N-CAM or L1 isoform" production by "NG108-15 cells *in vitro*" would be any indication for "treating/preserving motor function/restoring motor function" in a mammal afflicted with ALS or spinal cord injury, as currently recited. The methods are, therefore, incomplete for omitting essential steps, in which such omissions amount to a gap between the steps. See MPEP § 2172.01. The omitted steps are when "treating/preserving motor function/restoring motor function" is completed, as recited in the preambles.

7. Claims 94, 96-97, 99-100 & 102-104 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because CDMP2 on page 23 appears to indicate that CDMP2 is equivalent to BMP2A and/or BMP2B; thereby, reciting duplicative members of the Markush group.

8. Claims 82, 84-88, 90-91, 93 & 103-104 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the recitation of a " % identity/homology" is indefinite.

In particular, it is not known what is envisioned to meet this limitation, since the algorithm used to calculate the percent identity, or those parameters (e.g., gap penalties, mismatch penalties) required to determine such, are not disclosed within the specification. For example, different sequences contain different numbers of amino acid residues (i.e., including additions, substitutions, deletions and truncations), and it remains unclear how such differences in numbers of amino acid residues are to be calculated into a "% homology".

9. Claims 103-104 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because they are dependent on non-elected base claims.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Therefore, the priority date of the instant application is held to be 09/25/97, because the disclosure within the parent applications were clearly not sufficiently enabled to comply with the requirements of the first paragraph of 35 U.S.C. 112, as extensively prosecuted in these parent applications for treating any neurodegenerative disease state, or for use of the novel dor3 morphogen.

Claims 82, 84-88, 90-91, 93 & 103-104 are rejected under 35 U.S.C. 102(b) as being anticipated by The Regents of the University of California/Harland et al. (WO 95/06656; Ref #B5).

Harland et al. disclose a method of enhancing survival of nerve cells in a mammal, and treatment of ALS (i.e., restoring/preserving motor function) and "other conditions characterized by necrosis or loss of neurons, whether central, peripheral or motorneurons" (i.e., including the motorneurons affected during spinal cord injury), and "nerves damaged by traumatic conditions..., and the toxic effects of chemotherapeutics" (i.e., including mechanical/tumor-induced and chemical injury; as it relates to claims 85-87) through administering the morphogen, dor3, which inherently has at least 70% homology to... residues 330-431 of SEQ ID NO: 2 (e.g., pgs. 13-14); thereby, meeting all current structural limitations of the claims.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
March 1, 1999

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